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L-ASCORBIC ACID DERIVATIVE
[L-Asukorubinsan Yudotai]

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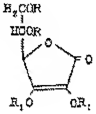
Specification

1. Title of the invention

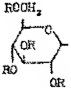
L-Ascorbic Acid Derivative

2. Claims

1. A L-ascorbic acid derivative represented by a general formula (I)



(in the formula, R represents hydrogen or a protective group of a hydroxyl group; R_1 represents hydrogen atom, lower alkyl group, benzyl group, or a residue represented by a formula (II)



[1] Numbers in the margin indicate pagination in the foreign text.

(in the formula, R has the same meaning as the above-mentioned one and may be the same or different); and at least one of R_1 represents a residue represented by the formula (II)).

2. The L-ascorbic acid derivative of Claim 1, characterized by the fact that two R in the general formula (I) represent one alkylene group.

3. <u>Detailed explanation of the invention</u>

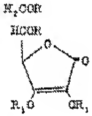
The present invention pertains to a L-ascorbic acid derivative. Specifically, the present invention pertains to a derivative in which L-ascorbic acid and glucose are bonded.

It is well known that L-ascorbic acid is an essential nutrient as vitamin C for human beings. However, it is also well known that the L-ascorbic acid is very easily oxidized and its effect is apt to be reduced when it is used for chemicals. For this reason, many researches on the stability of the L-ascorbic acid are conducted, however there is still no sufficient method.

These inventors considered the above-mentioned situation and researched the above problems in earnest, and

as a result, a new L-ascorbic acid derivative was successfully manufactured. Then, the present invention was completed.

In other words, the essence of the present invention pertains to a L-ascorbic acid derivative represented by /2 a residue represented by a general formula (I)



(in the formula, R represents hydrogen or a protective group of a hydroxyl group; R_1 represents hydrogen atom, lower alkyl group, benzyl group, or a residue represented by a formula (II)

(in the formula, R has the same meaning as the above-mentioned one and may be the same or different); and at

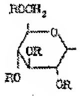
least one of R_1 represents a residue represented by the formula (II)).

Next, the present invention is explained in detail.

In the above-mentioned general formula (I), R represents a hydrogen or a protective group of a hydroxyl group. As the protective group of the hydroxyl group, well-known protective groups, for example, acyl group such as acetyl, trifluoroacetyl, trichloroaetyl, benzoyl, and p-nitrobenzoyl, hydrocarbon group such as methyl and benzyl are mentioned. Also, two R may represent one alkylene group such as 1,1-ethylene, 2,2-propylene, and 2.2-butylene groups.

R is preferably a hydrogen atom since the compound of the present invention exerts an effect as vitamin C.

Also, R_1 represents hydrogen atom, lower alkyl group, benzyl group, or a residue represented by the formula (II)



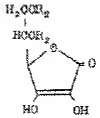
(in the formula, R has the same meaning as the above-mentioned). As the lower alkyl group, for example, methyl, ethyl group, etc., are mentioned. As the residue

represented by the formula (II), D-glucopyranosyl, 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl, 2,3,4,6-tetra-O-benzoyl-D-glucopyranosyl, 2-benzoyl-3,4,6-tri-O-acetyl-D-glucopyranosyl, 2,3,4,6-tetra-O-methyl-D-glucopyranosyl, 2,3,4,6-tetra-O-methyl-D-glucopyranosyl, 2,3,4,6-tetra-O-benzyl-D-glucopyranosyl, 2,3,4,6-di-D-ethylidene-D-glucopyranosyl, etc., can be mentioned. The residue represented by the formula (II) is usually bonded at β coordination.

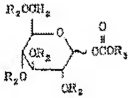
As the ascorbic acid derivative represented by the general formula (I), for example, 2,3-di-O-(β-D-glucopyranosyl)-L-ascorbic acid, 2-O-(β-D-glucopyranosyl)-L-ascorbic acid, 3-O-(β-D-glucopyranosyl)-L-ascorbic acid, 2,3-di-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2,3-di-O-(β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2-O-(β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-3-O-(β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2,3-di-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 2-O-methyl-3-O-(β-D-glucopyranosyl)-L-ascorbic acid, 3-O-methyl-2-O-(β-D-

glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2-O-methyl-3-O-(β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2-O-methyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 2-O-benzyl-3-O-(β-D-glucopyranosyl L-ascorbic acid, 3-O-benzyl-2-O-(β-D-)- /3 glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2-O-benzyl-3-O-(β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2-O-benzyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 5,6-di-O-acetyl-2,3-di-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, 5,6-di-O-benzoyl-2,3-di-O-(2,3,4,6-tetra-O-benzoyl-2,3-di-O-benzoyl-β-D-glucopyranosyl)-L-ascorbic acid, 5,6-O-isopropylidene-2,3-di-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid, etc., can be mentioned.

The L-ascorbic acid derivative of the present invention can be manufactured by the following method, for instance. In other words, this ascorbic acid derivative can be obtained by reacting a L-ascorbic acid, in which hydroxyl groups at 5 and 6-positions are protected, represented by a general formula (III)



(in the formula, R_2 represents a protective group of a hydroxyl group) and carbonic ester at 1-position of D-glucopyranose represented by a general formula (IV)



(in the formula, R_2 has the same meaning as the above-mentioned one, and R_3 represents a hydrocarbon group or hydrocarbon halide group). If the hydroxyl group at 2-position or 3-position of the reaction product is alkyl-etherified with diazoalkane or dialkylsulfuric acid and if necessary, the protective group of the hydroxyl group is eliminated by a well-known method, the ascorbic acid derivative represented by the general formula (I) can be obtained.

As R_2 in the general formula (III) and (IV), a group similar to the protective group of the above-mentioned hydroxyl group can be mentioned. Also, as R_3, alkyl group having about 1-10 carbons such as methyl, ethyl, propyl,

isopropyl, butyl, sec-butyl, and t-butyl, aryl group such as phenyl, alkyl halide group such as trifluoroethyl and trichloroethyl, etc., can be mentioned.

The L-ascorbic acid, in which the hydroxyl groups at 5 and 6-positions are protected, represented by the general formula (III), for example, is manufactured by reacting L-ascorbic acid and acetone saturated with hydrogen chloride (see Experientia, Vol. 19, pp.619 (1963)).

The carbonic ester at 1-position of the glucopyranose represented by the general formula (IV), for example, can be manufactured by reacting a sugar, in which hydroxyl groups other than the hydroxyl group at 1-position such as 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose are protected, and the corresponding halogenated carbonic ester such as phenyl chlorocarbonate in the presence of a base such as pyridine. As the carbonic ester at 1-position of the glucopyranose, there are α-body and β-body, and any of them can be used.

The method for reacting the L-ascorbic acid, in which the hydroxy groups at 5 and 6-positions are protected, and the carbonic ester at 1-position of glucopyranose is not particularly limited. In reacting both of them, the mol ratio of both of them is not particularly limited, either. If both of them are reacted at each nearly equal equivalent, a reaction product of 1:1 is mainly attained,

and if the carbonic ester at 1-position of the glucopyranose is used at twice equivalent or more, a reaction product of 1:2 is mainly obtained. In this case, the reaction product of 1:1 is mainly a product in which glucopyranose is bonded at 3-position of L-ascorbic acid.

In obtaining a product in which glucopyranose is bonded only at 2-position of L-ascorbic acid, a hydroxyl group at 3-position is alkyl-etherified in advance by reacting L-ascorbic acid and diazoalkane at low /4 temperature and reacted with carbonic ester at 1-position of glucopyranose.

During the reaction, if a nonprotic solvent inactive to the reaction, such as chlorobenzene, propionitrile, and nitromethane is used, desirable results are given.

The reaction temperature is usually 60-150°C, preferably 80-130°C.

The reaction time depends on the reaction temperature and the kind of raw material, however the reaction temperature is about 2-6 h.

During the reaction, since the generation of a gas is seen by a decarboxylation reaction, the reaction may be carried out until the gas generation finishes or a theoretical amount of gas is generated.

The reaction system may be at normal pressure or can also be under reduced pressure. If the reaction system is under reduced pressure, the side reaction is reduced, which is preferable. The reduced pressure may be about 100 mmHg, however about 20-30 mg is preferable.

In alkyl-etherifying a hydroxyl group at 2-position or 3-position of this product, it may be reacted with diazoalkane such as diazomethane, dialkylsulfuric acid such as dimethylsulfuric acid, etc., by an ordinary method.

Also, the protective groups of the hydroxyl groups may be eliminated by applying a well-known method to each protective group. However, it is necessary to carry out the elimination under the condition of basicity, neutrality, or weak acidity so that glycoside bonds of the ascorbic acid are not cut.

Thus, after manufacturing the ascorbic acid derivative, it can be purified and isolated by the combination of well-known purification means such as solvent distilling-off, recrystallization, filtration, column chromatography treatment, activated carbon treatment, etc.

Since the compound of the present invention has a biological activity as vitamin C and the stability to the oxidation is improved, it is usable for drugs, etc.

At the same time, in the compound of the present invention, since its constitutional components are natural products, the toxicity is little recognized.

Next, the present invention is explained in further detail by application examples, however the present invention is not limited at all to the following application examples unless its essence is deviated.

Application Example 1

940 mg (2 mmol) 2,3,4,6-tetra-O-acetyl-1-O-phenoxycarbonyl-β-D-glucopyranose and 475 mg (2.2 mmol) 5,6-O-isopropylidene-L-ascorbic acid manufactured by a method described in the specification of Japanese Patent Application No. Sho 51[1976]-19791 were melt-reacted at 120-130°C for 3 h under reduced pressure by an aspirator. When the reaction mixture was separated by a silica gel column chromatography (chloroform), 246 mg (28%) 5,6-O-isopropylidene-2,3-di-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid (hereinafter, called (A)) and 625 mg (57%) 5,6-O-isopropylidene-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid (hereinafter, called (B)) were obtained.

Properties of (A):

m.p. 95-97°C (recrystallized from ethanol-ethyl ether)

$[\alpha]^{22}_{D} = -12°$ (C 1, chloroform)

Element analysis value

Calculated value as $C_{37}H_{48}O_{26}$: 50.68% C, 5.51% H

Measured value: 50.68% C, 5.48% H

^{13}C-NMR ($CDCl_3$, δ value, ppm) C-1 of glucose 98.4, 96.4

Properties of (B):

m.p. 157-160°C (recrystallized from ethanol-ethyl ether)

$[\alpha]^{22}_{D}$ = +16° (C 0.5, chloroform)

Element analysis value

Calculated value as $C_{23}H_{30}O_{18}$: 50.54% C, 5.53% H

Measured value: 50.27% C, 5.48% H

^{13}C-NMR ($CDCl_3$, δ value, ppm) C-1 of glucose 98.8; C-2 70.9; C-3 73.4; C-4 68.1; C-5 72.4; C-6 61.6

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Application Example 2

579 mg (1.1 mmol) 2,3,4,6-tetra-O-acetyl-1-O-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranose and 109 mg (0.5 mmol) 5,6-O-isopropylidene-L-ascorbic acid manufactured by the method described in the specification of Japanese Patent Application No. Sho 51[1976]-19791 were melt-reacted at 135-140°C for 4 h under reduced pressure by the aspirator. The reaction mixture was posttreated similarly to Application Example 1, so that (A) was obtained at a yield of 62%.

Application Example 3

263 mg (0.5 mmol) 2,3,4,6-tetra-O-acetyl-1-O-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranose and 133 mg (0.6 mmol) 5,6-O-isopropylidene-L-ascorbic acid were melted in 4 mL nitromethane and heated and refluxed at normal pressure for 4 h. The reaction product was enriched under reduced pressure and posttreated similarly to Application Example 1, so that 14 kg (6%) (A) and 164 kg (60%) B were obtained.

Application Example 4

262 mg (0.5 mmol) 2,3,4,6-tetra-O-acetyl-1-O-(2,2,2-trichloroethoxycarbonyl)-β-D-glucopyranose and 147 mg (0.7 mmol) 5,6-O-isopropylidene-L-ascorbic acid were melted in 4 mL nitromethane and heated and refluxed at normal pressure for 6 h. An excessive amount of diazomethane was added to the reaction product, held at room temperature for 1 h, and posttreated similarly to Application Example 3, so that 203 mg (72%) 5,6-O-isopropylidene-2-O-methyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-L-ascorbic acid was obtained.

Amorphous, $[\alpha]^{22}_{D} = -6^{\circ}$ (C 1.7, chloroform)

Element analysis value

Calculated value as $C_{24}H_{32}O_{15}$: 51.42% C, 5.75% H

Measured value: 51.23% C, 5.79% H

^{13}C-NMR ($CDCl_3$, δ value, ppm) C-1 of glucose 98.7; C-2 70.9; C-3 73.3; C-4 68.3; C-5 72.2; C-6 61.8

^{1}H-NMR ($CDCl_3$, δ value, ppm): 3.93 (-C-CH_3)